Original articles

Long term prognosis of patients with cystic fibrosis in relation to early detection by neonatal screening and treatment in a cystic fibrosis centre

Jeannette E Dankert-Roelse and Gerard J te Meerman

Abstract

***Background* – A study was undertaken to evaluate whether an early diagnosis by neonatal screening may improve the long term prognosis of patients with cystic fibrosis and to assess the influence of expert management started immediately after the diagnosis.**

***Methods* – Comparative clinical follow up in three birth cohorts of patients with cystic fibrosis was performed at the Cystic Fibrosis centre in Groningen in close collaboration with paediatricians in general hospitals in the north-eastern part of the Netherlands. The first birth cohort (n = 19) was detected by screening and the two other cohorts were detected clinically, one (n = 30) consisting of patients born during the screening programme and the other (n = 32) of patients born during the six years immediately after the screening programme ended. The total number of patients in the three birth cohorts included all patients with cystic fibrosis born in this area during a 12 year period. Cumulative survival rates and the variation with time of lung function, the levels of immunoglobulins, and growth patterns were used as main outcome measures.**

***Results* – Patients born during the screening programme but detected clinically appeared to have a reduced life expectancy compared with patients detected by screening. The patients detected by screening showed less deterioration in lung function (annual decrease 1·2% of FEV_1 % pred), a smaller increase in immunoglobulin levels, and minimal catch-up growth compared with an annual decrease of 3·25% of FEV_1 % pred in the non-screened birth cohort of the same age, a higher rise in immunoglobulins leading to increased levels at the end of the observation period, and catch-up growth for weight as well as height. Differences between patients treated in a cystic fibrosis centre and those not referred to a specialist centre were smaller but similar, in favour of treatment at a cystic fibrosis clinic.**

***Conclusions* – Expert management started immediately after an early diagnosis of cystic fibrosis by neonatal screening results in important beneficial effects on the outcome and clinical course of the condition. The institution of very early treatment may be critical for the outcome and long term prognosis for most patients with cystic fibrosis. Neonatal screening programmes for cystic fibrosis should be introduced more widely.**

(*Thorax* 1995;50:712-718)

Keywords: cystic fibrosis, neonatal screening, cystic fibrosis centres.

Department of Paediatrics, Paediatric Pulmonology
J E Dankert-Roelse

Department of Medical Genetics
G J te Meerman

University of Groningen, The Netherlands

Reprint requests to:
Dr J E Dankert-Roelse, Department of Paediatrics, Free University, PO Box 7057, 1007 MB Amsterdam, The Netherlands.

Received 24 November 1994
Returned to authors 23 January 1995
Revised version received 16 February 1995
Accepted for publication 21 February 1995

Cystic fibrosis is one of the commonest inheritable diseases among white people. Without treatment most patients with this disease will die in infancy or early childhood.[1] At present the pulmonary problems in general determine the morbidity and the mortality of patients with cystic fibrosis. Most of the pulmonary damage is not due to the primary defect but arises secondarily due to the increased susceptibility to respiratory infection. The present therapeutic strategies developed over the past 30 years have dramatically improved the life expectancy of patients with cystic fibrosis. For babies born today with cystic fibrosis the predicted mean life expectancy is about 40 years.[2] It is conceivable that the present therapeutic strategies applied before irreversible airways damage has occurred will have an added favourable influence on outcome and quality of life of patients with cystic fibrosis. Diagnosis as early as possible – for example, by neonatal screening – may be necessary for effective therapeutic interventions aimed at preventing irreversible damage to the airways. Results of earlier studies have suggested that early diagnosis by neonatal screening and early treatment may reduce mortality and morbidity of patients with cystic fibrosis.[3,4] Another major factor in improving survival is the increasing centralised care of cystic fibrosis.[5]

In the present study earlier observations were extended over a longer period and a greater number of patients. While in our earlier studies

Table 1 Composition of the three patient groups

	S	*Non-S*	*Post-S*
Year of birth	1973–9	1973–9	1979–85
Diagnosis by screening	19	—	—
Diagnosis by symptoms	(5)*	25+5*	32
Meconium ileus	4	2	9
In survival analysis	15	28	20
Lost to follow up	2	1	5
Death before the start of study	4	5	1
In clinical follow up	13	24	26

S = patients detected by screening; non-S = patients detected by clinical symptoms; post-S = patients born after the end of the screening programme detected by clinical symptoms.
* Patients born in screened birth cohort with false negative screening test.

only observations at a certain age on a cross sectional basis were reported, in this study all data collected over a 10 year period were evaluated. The aim of this longitudinal study was to investigate whether intensive management started immediately after a diagnosis of cystic fibrosis by neonatal screening favourably influences the outcome and clinical condition of these patients in the long term.

Methods

PATIENTS

An experimental neonatal screening programme for cystic fibrosis using the determination of the albumin content of meconium was carried out in the north of the Netherlands between March 1973 and March 1979.[6] Forty five percent of all neonates in this area were involved in the screening programme; the remaining 55% were not screened. All patients with cystic fibrosis born during this period were registered centrally based on annual inquiries by all paediatricians practising in this area. Survival and clinical outcome up to the age of 11 years in the patients in the screened and non-screened birth cohorts have been described elsewhere.[3]

In the present analysis three birth cohorts of patients with cystic fibrosis were compared. Data on the composition of these three patient groups are summarised in table 1. The first group consisted of 18 patients with cystic fibrosis detected by neonatal screening between 1 March 1973 and 1 March 1979, plus one patient detected between 1 March 1979 and 30 June 1979 (S group). Five patients from the screened birth cohort had false negative screening tests and a diagnosis of cystic fibrosis was made later on a clinical basis. The age at diagnosis varied from four months to 10 years in these five patients who were therefore analysed with the 25 patients born in the same period and the same area but detected by clinical symptoms (non-S group). Three patients were lost to follow up, two from the screened group and one from the non-screened group. No clinical data were obtained from four patients in the screened group and five in the non-screened group, eight of whom died in the first year of life as previously described.[7] In one patient in the non-screened group who died at the age of nearly three years a diagnosis of cystic fibrosis was made retrospectively. Longitudinal clinical evaluations were performed in 13 patients in the screened group and 24 in the non-screened group. One of the 24 patients in the non-screened group preferred treatment at the local hospital. Information on the clinical course of this patient was provided later.

The third birth cohort consisted of patients with cystic fibrosis born in the same region between 1 July 1979 and 1 January 1986, immediately after the closure of the experimental screening programme (post-S group). With the help of the national Dutch Cystic Fibrosis Registry, started in 1983, the patients born in the six year period after the screening programme ended were identified. The Dutch Cystic Fibrosis Registry periodically asks all Dutch paediatricians and pulmonologists to report their patients with cystic fibrosis.[8] The registry revealed no unknown patients with cystic fibrosis born in the period 1973–9, confirming that all patients currently diagnosed with cystic fibrosis are included in the study. In total, 32 patients with cystic fibrosis born between 1979 and 1985 were identified before 1 December 1989 (the closing date of the study). None was detected by neonatal screening. Nine of these 32 patients were not known in the Cystic Fibrosis centre at Groningen. Of these patients, one died at the age of 16 days before referral to a Cystic Fibrosis centre, four were referred to another centre in the Netherlands, and four were treated solely at the local hospital. Of these latter eight patients three were assessed only once or twice at the Cystic Fibrosis centre of the University Hospital in Groningen, and clinical data of three patients were obtained retrospectively from the local hospital. The parents of two patients refused to cooperate in the study. Three patients had to be excluded from the study as other health problems dominated over their cystic fibrosis. The other diagnoses in these patients were congenital heart disease, severe spastic tetraplegia after a very premature birth, and one patient developed a bowel dysfunction after surgical treatment for ileal atresia leading to death at the age of six months. Thus, a total of five patients could not be included in the study, resulting in 27 patients in the post-S group. In one patient a diagnosis of cystic fibrosis was made at the age of 4·5 years and only one observation was made before the study closed.

In all patients entering the study the diagnosis of cystic fibrosis was confirmed by the quantitative pilocarpine iontophoresis test. In three children who were identified by screening and treated only in local hospitals the diagnosis could not be confirmed when a repeat sweat test was performed. Patient data were analysed to evaluate the influence of a very early diagnosis and treatment on outcome and clinical course. To assess also the influence of treatment at a specialised cystic fibrosis centre all clinical data obtained in patients not referred to a cystic fibrosis centre or during the first six months after referral to the centre were analysed and compared with the clinical observations collected during the period of treatment at the centre. The investigator regularly visited the paediatricians caring for the patients not being treated at a specialist centre to collect data. Discussions were held concerning the course of disease and advice was given on treatment options.

Table 2 Relations between birth cohort and age at diagnosis, percentage of patients with meconium ileus and frequency of cystic fibrosis (CF) at birth

	S	*Non-S*	*Post-S*
Median age at diagnosis (months)	<1	14	23
% of patients with meconium ileus	16·7	8	28·1
Frequency of CF at birth	1:4089	1:4873	1:7000*

S = patients detected by screening; non-S = patients detected by clinical symptoms; post-S = patients born after the end of the screening programme detected by clinical symptoms.
* Estimated frequency at birth based on the number of births in the area (data derived from the Dutch Central Bureau of Statistics).

CLINICAL FOLLOW UP

The clinical follow up study started on 1 April 1980 and ended on 1 December 1989.[3] All patients in the three groups referred to the Cystic Fibrosis centre in Groningen participated in the clinical follow up immediately after diagnosis and/or referral. All data collected between 1 April 1980 and the closing date of the study (1 December 1989) were used for clinical evaluations. Clinical assessments were performed at six monthly intervals as previously described.[3] Nine patients were examined in the local hospitals once or twice a year. Of four patients not known to the centre, data were obtained retrospectively in 1989.

CLINICAL VARIABLES

Clinical data obtained on growth (height and weight), lung function, immunological status, and sputum bacteriology were analysed.

Growth

Height and weight were measured at each visit to the clinic. Standard deviation scores (SDS) for height and weight were compared with the 50% percentile for height and the mean weight of Dutch children of the same age and sex as standards.[9]

Lung function

Inspiratory vital capacity (VC), forced expiratory volume in one second (FEV_1), both expressed as a percentage of predicted control values based on patient height, age and sex,[10] were used as parameters.

Immunology

Immunoglobulins A, M, G, and E were determined routinely at six month intervals.

Sputum bacteriology

Sputum samples or tracheal aspirates were taken at each clinic visit. Patients were considered to be chronically colonised when the same microorganism was found on two consecutive clinic visits.

STATISTICAL METHODS

Cumulative survival rate

A cumulative survival analysis by the life table method was calculated for the three groups from the date of birth to the closing date of the study on 1 December 1989.[11] Fifteen patients with meconium ileus (or related problems such as ileal or jejunal atresia), four patients in the S group, two in the non-S group, and nine in the post-S group, were excluded from the survival analysis (table 1). A survival analysis was therefore calculated on 15 patients in the S group, 28 in the non-S group, and 20 in the post-S group. Differences in survival rate were calculated by means of the Fisher exact probability test.

Multivariate regression analysis

Patient data were compared by means of a multivariate regression analysis (SYSTAT, MGLH module). Regression coefficients for each clinical variable with time were calculated for each group. The statistical comparison of screening compared with non-screening was performed by calculating the interaction between age and screening or non-screening for the regression coefficients. The significance of differences between regression lines was tested with a general linear model.

In a similar way the influence of specialist centre treatment versus non-centre treatment was evaluated.

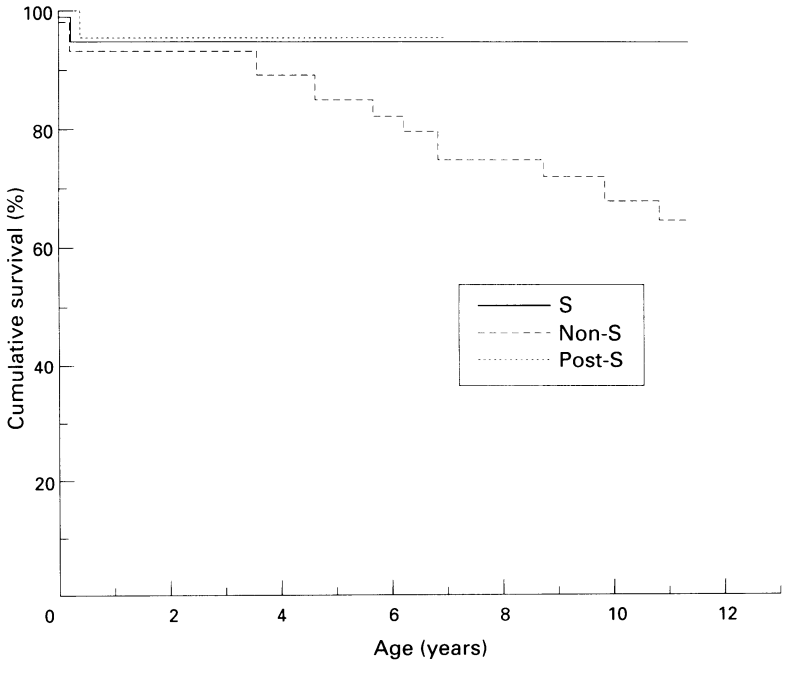

Figure 1 Cumulative survival rate (%) of patients detected by screening (S, n = 15), and those detected by symptoms born 1973–9 (non-S, n = 28) and 1979–86 (post-S, n = 20).

Results

INFLUENCE OF THE SCREENING PROGRAMME ON AGE AT DIAGNOSIS

Comparison of the median age at diagnosis and the frequency of cystic fibrosis at birth revealed that the age at diagnosis in the group of patients born during the six years after the screening programme had ended was even higher than in both birth cohorts born earlier, and that the observed frequency at birth was considerably lower (table 2). This indicated that, at the closure of the study, not all patients with cystic fibrosis from the area were detected. The high percentage of patients with meconium ileus (who are usually recognised immediately as patients with cystic fibrosis) in the youngest group of patients was another indication that

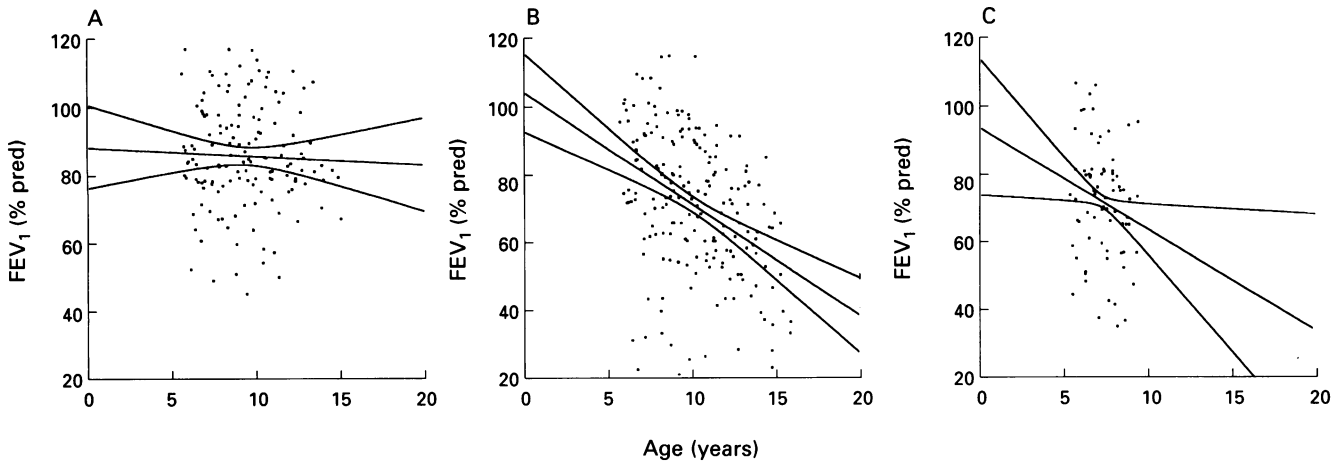

Figure 2 Variation in mean FEV_1 (%pred) with regression lines (with 90% confidence intervals) with time in (A) patients detected by screening, (B) those born between 1973 and 1979 detected by symptoms, and (C) those born between 1979 and 1986 detected by symptoms.

the diagnosis of cystic fibrosis without screening was missed for some time in a large number of patients.

CUMULATIVE SURVIVAL ANALYSIS

The cumulative survival rate was 94% for the screened patients and 65% for the non-screened patients at the age of 11 years, excluding the patients with meconium ileus ($p<0.05$, Fisher's exact probability test). There was a remarkable difference between these two survival curves (fig 1); in the screened group only one patient died at a very young age and no deaths occurred subsequently. In the non-screened group a high mortality rate was found in the first year of life, but by the fourth year of life the life expectancy appeared to be reduced. For the patients born later (post-S group) the observation period was too short for a reliable calculation over the age of seven years to be made. At that age 95% of the patients were still alive, the one death in this group occurring before the diagnosis of cystic fibrosis was made. The survival curve was closer to that of the S group than to the non-S group. For the younger patients life expectancy was improved compared with 10 years earlier, and this observation has also been made in other western European countries.[12]

Table 3 Regression with time of forced expiratory volume in one second (FEV_1), expressed as a percentage of predicted values, corrected for age differences between groups

Patient group (no. of observations)	*Coefficient of regression (mean (SE))*	*F ratio*	*p*
S (142)	−1.2 (0·45)	7·41	<0·01
Non-S (197)	−3·25 (0·34)	89·52	<0·001
Post-S (73)	−2·6 (1·42)	3·35	NS

S = patients detected by screening; non-S = patients detected by clinical symptoms; post-S = patients born after the end of the screening programme detected by clinical symptoms.

Table 4 Analysis of variance for multivariate regression analysis of the forced expiratory volume in one second (FEV_1), expressed as a percentage of predicted values, after correction for age differences between patient groups

	Sum of squares	*Degrees of freedom*	*Mean square*	*F ratio*	*p*
Age	2520·45	1	2520·45	21·59	<0·001
Age × group	1521·10	2	760.55	6·52	<0·005
Error	47623·19	408	116·72		

CLINICAL VARIABLES

Lung function

A comparison of the observed FEV_1 (%pred) showed that patients in the screened group maintained the same levels of lung function throughout the observation period (coefficient of regression −0·24 (0·6)), while patients in the non-S and post-S groups showed a statistically significant decrease in lung function with increasing age (coefficients of regression −3·2 (0·5) and −2·9 (1·8), respectively) (fig 2). However, the two oldest birth cohorts differed slightly in age because of the late detection and early death of some patients in the non-S birth cohort, and the data of the post-S group were mostly obtained at a younger age. To adjust for bias due to a possible effect of age a correction was necessary for the comparison of the lung function. By shifting the time scale the mean age of each individual at observation was set to 0; similarly, the mean FEV_1 (%pred) was shifted so that each person had a mean value of 0. Only patients with at least two observations (mean number of observations nine per patient, but in the post-S group only five) could be included in this adjustment (S: n = 13, non-S: n = 18, post-S: n = 13). The regression was analysed for each group. After this age-adjusted correction the deterioration in lung function in the screened group was considerably less (1·2% annual decrease) than in the non-screened group (3·25% annual decrease). Although the post-screening group showed a mean decrease of 2·6%, the number of observations was probably too small to find a significant regression (tables 3 and 4).

Immunology

IgG levels can be considered markers of the degree of inflammation and may therefore be used as an indicator of the severity of chronic lung infection. In table 5 it can be seen that the IgG levels increased with age in both the non-S and post-S groups but not in the S group.

Microbiology

There were no differences in the chronic colonisation with *Staphylococcus aureus* in the S

Table 5 Effects of neonatal screening expressed as mean (SD) differences in coefficients of regression with age

Variable	S	Non-S	Post-S	p*
VC (%pred)	−0·39 (0·46)	10·6 (10·0)	−0·99 (1·35)	NS
IgG	0·68 (11)	72 (14)	101 (14)	<0·0001
IgE	−19·13 (7·43)	18·45 (11·56)	0·89 (7·6)	0·02
SDS weight	0·028 (0·021)	0·048 (0·016)	0·17 (0·02)	<0·0001
SDS height	0·041 (0·027)	0·098 (0·016)	0·19 (0·025)	<0·0001

S = patients detected by screening; non-S = patients detected by clinical symptoms; post-S = patients detected by clinical symptoms born after the end of the neonatal screening programme; VC (%pred) = vital capacity, expressed as a percentage of predicted values; IgG = immunoglobulin G (mg/dl); IgE = immunoglobulin E (units/l); SDS weight = standard deviation score for weight; SDS height = standard deviation score for height.
* p value for the multivariate regression analysis calculated from the statistical interaction of the factors screening and age.

Table 6 Cumulative prevalence of chronic colonisation with Staphylococcus aureus and Pseudomonas aeruginosa up to the age of 12 years

	S	Non-S	p (χ^2 test)
S aureus	10/13	19/24	NS
P aeruginosa	2/13	12/23	<0·05

S = patients detected by screening; non-S = patients detected by clinical symptoms.

and non-S groups. However, up to the age of 12 years relatively more non-screened patients appeared to be chronically colonised with *Pseudomonas aeruginosa* (table 6). For the post-S group, and after the age of 12 years, insufficient data were available for a reliable comparison to be made.

Growth and nutritional status

Standard deviation scores (SDS) for height and weight for the three groups are shown in table 5. At the start of the study the height of the patients in the screened group was just below the population mean values, and at the end of the study around the expected level. The mean weight remained about half a standard deviation under the mean levels throughout the observation period. However, these patients were born in the 1970s and were mostly fed with a fat restricted diet until the beginning of the 1980s. The patients in the non-S and the post-S groups showed a greater growth retardation for both height and weight than those in the S group. However, data collection for the post-S patients often started immediately after diagnosis while for most patients in the other groups it began some time after diagnosis. Most catch-up growth will occur shortly after diagnosis, and this probably contributed to the larger differences of trends observed in the post-S group.

Table 7 Effects of treatment at a specialist cystic fibrosis centre expressed as mean (SD) differences in coefficients of regression with age

Variable	C	Non-C	p*
FEV_1 (%pred)	−2·08 (0·36)	−5·32 (3·1)	NS
IgG	65·83 (7·33)	148·98 (31.24)	0·001
SDS weight	0·039 (0·01)	−0·007 (0·03)	NS
SDS height	0·06 (0·01)	0·066 (0·03)	NS

C = patients treated for at least six months at or in cooperation with a cystic fibrosis centre; non-C = patients treated solely at the local hospital. For definition of other abbreviations see footnote to table 5.
* p value for the multivariate regression analysis calculated from the statistical interaction of the factors centre treatment and age.

MULTIVARIATE REGRESSION ANALYSIS

Screening versus non-screening

The coefficients of regression for the FEV_1 (%pred) after correction for the differences in age are shown in table 3. The results of the analysis of variance calculated for the FEV_1 (%pred) after correction for age differences are summarised in table 4. The coefficients of regression and the results of the analysis of variance for screening or non-screening are shown for the clinical variables VC (%pred), IgG, IgE, and the SDS for height and weight for the three patient groups (table 5). With the exception of VC (%pred), these coefficients differed considerably in the comparison of screening with non-screening. The observed differences were statistically significant when calculated by multivariate analysis (p values in table 5).

Centre treatment versus non-centre treatment

A second similar multivariate regression analysis was made with the aim of assessing whether treatment at a specialist cystic fibrosis centre leads to a better clinical course (table 7). The observed differences were smaller than when comparing screening and non-screening. A greater decrease in lung function was seen in the patients not treated at a specialist centre, but the difference was not statistically significant, probably due to lack of statistical power. We assume this to be the case from the significantly different IgG levels which is another marker of lung infection. Patients treated at a specialist centre showed a greater increase in weight than those treated elsewhere.

The analysis of centre treatment versus non-centre treatment was not quite independent from the demonstrated differences in the analysis of screening versus non-screening. Screened patients were referred more often to the centre to confirm the diagnosis than non-screened patients; 47% of screened patients were known at the centre before the start of the study compared with only 25% of the non-screened patients. However, in later years the rate of referral increased, with 75% of the post-S patients being referred to a cystic fibrosis centre immediately after diagnosis.

Discussion

OUTCOME AND CLINICAL ASSESSMENT

The reduced life expectancy and the non-reversible downward development of the mean (SE) FEV_1 of 3·24 (0·34)% per annum in the non-screened group (detected on a clinical basis) was significant. However, in the patients detected by neonatal screening a lesser degree of deterioration of 1·2 (0·45)% occurred, indicating that a favourable outcome and long term prognosis can be achieved by intensive management of patients with cystic fibrosis if started as soon as the diagnosis is confirmed after identification by neonatal screening. However, for many of the patients in the non-S group the 30% FEV_1 (%pred) threshold that is considered to require lung transplantation would be reached more rapidly due to the rate of progression of the disease.[13]

Pseudomonas aeruginosa most often colonises the airway epithelium after it has been damaged. The finding that the inflammatory process continues once colonisation and infection by *P aeruginosa* has been established in the lower airways[14] may explain the more rapid deterioration in lung function found in the non-screened patients, who showed a higher percentage of persistent colonisation with *P aeruginosa* at a younger age than the patients detected by screening. A direct relation between the incidence of *P aeruginosa* colonisation, the extent of pulmonary disease, and the level of serum immunoglobulins has been observed.[15] In our study IgG levels rose significantly faster in patients in the non-S and post-S groups than in those in the S group. The more rapidly increasing levels of immunoglobulin G in the younger age (post-S) group compared with the patients identified by screening can only partly be explained by the fact that these levels were monitored from a younger age than in the screened group. At the age of seven the levels were higher than expected and certainly higher than in the patients diagnosed by screening, suggesting that more inflammatory damage in the airways had already occurred in these patients and this may be a risk factor for colonisation with *P aeruginosa* at an early age. A longer follow up of this patient group is needed as not all patients were diagnosed in this group. Although no differences in colonisation by *S aureus* were found, intensive antibiotic treatment during exacerbations from early infancy may have minimised the extent of airway damage and inflammation and perhaps delayed colonisation by *P aeruginosa*. More effective inhibition of colonisation may be achieved by treatment with continuous flucloxacillin started after neonatal diagnosis, as shown in a prospective study on the effects of neonatal screening in which a lower colonisation rate of the upper respiratory tract with *S aureus* was reported at the age of two years, while in infants not given oral prophylaxis there was an association between carriage of *S aureus* and subsequent colonisation with *P aeruginosa*.[16]

Severe growth retardation was present at diagnosis in most patients detected clinically in both the non-S and post-S groups. The catch-up growth after diagnosis shown by these patients results in similar nutritional status at the end of the observation period, whether the diagnosis was made by screening or clinically. Considerably less catch-up growth was noted in the patients detected by screening. In other studies the nutritional deficiencies already seen at the diagnosis of cystic fibrosis in infants detected by screening[17] were rapidly reversed after an early diagnosis.[18] This difference may have an important effect on outcome since normal growth patterns during childhood in patients with cystic fibrosis have been shown to benefit survival.[19]

SELECTION BIASES

A major drawback of the screening programme was the use of the meconium test which led to five patients from the screened birth cohort being undetected. As they were diagnosed clinically we decided to assess these patients with the non-S patients. Due to the long follow up period some losses to follow up were inevitable, but these were comparable in the three birth cohorts. A proportionally large number of patients died before the start of the study and/or before the age of six years (four in the screened group and 10 in the non-screened group), which could have introduced a selection bias. As the number of deaths in the non-screened group was higher than in the screened group, this bias could detect a more favourable course for the surviving patients in the non-screened group. However, the more rapid deterioration of lung function in the non-screened group persisted. Selection bias due to incomplete ascertainment in the screened and the non-screened cohorts was unlikely as the national Cystic Fibrosis Registry did not reveal any unknown patients with cystic fibrosis from this area. As the organisations that care for mother and child which decided whether to participate in the screening programme operate quite independently from hospital care in the Netherlands, selection bias due to differences in care of patients with cystic fibrosis between the birth cohorts is improbable. The only apparent selection bias was that paediatricians confronted with a neonate with meconium ileus often asked the laboratory to investigate a meconium sample, while otherwise the child would not have been screened. This probable selection bias was one reason for calculating a survival analysis with exclusion of patients with meconium ileus. Moreover, survival or early death due to complications of meconium ileus are probably more a reflection of the quality of surgical care than the result of a neonatal screening programme.

We think it improbable therefore that the differences observed are caused by chance alone. As the investigation encompassed the whole population of patients with cystic fibrosis in a well defined area during a 12 year period, the observed differences in survival and clinical status can only suggest that, without screening, a diagnosis of cystic fibrosis is often made at a stage of the disease when deterioration can no longer be prevented, despite intensive management.

STATISTICAL ANALYSIS

For long term development in a progressive disease the rate of progression may be more important than the mean differences at a certain age. We therefore used a statistical analysis which included calculation of trends. For the computation of the trend all data obtained from one subject were considered independently, while the variability in the number of data among individuals and their correlation would influence the reliability of the results regarding the mean. The statistical analysis of the trends could not be performed by comparing the individual regression coefficients. As for lung function, the variance of the regression coefficients was high due to the high intra-individual variability of the dependent variable

as large intra-individual differences in FEV_1 between consecutive visits were observed, probably due to exacerbations. By the correction made for possible age-related differences, these intra-individual differences were also minimised.

INFLUENCE OF TREATMENT AT A SPECIALIST CENTRE

Although less obvious, a favourable influence on the course of the disease was also observed by treatment at a specialist centre. Those treated at a cystic fibrosis centre had less severe lung infection and a greater increase in weight than those not treated at a specialist centre. As in other studies in which the influence of treatment at a specialist centre has been evaluated, less motivated parents were found to prefer to stay with the local hospital, and this may introduce a negative selection bias for the non-centre treated patients. As referral in many cases followed the investigation, only a small number of patients in our study never visited a cystic fibrosis centre. A selection of patient data was therefore used in the comparison of centre treatment versus non-centre treatment. Only those data collected in the first six months after referral and the data of the patients never referred to the centre (mostly obtained retrospectively) were used to minimise the influence of the study on the observations. This data selection probably has led to loss of statistical power.

In general, the investigation has resulted in all patients included in the study receiving optimal treatment, with the probable outcome that initial differences between patients due to treatment differences will diminish. Despite optimal treatment for all patients, the differences between the screened and non-screened patients persisted, indicating that delay in the start of treatment of patients with cystic fibrosis after the neonatal period can have a deleterious effect on further development of the disease. Our data suggest that early diagnosis and optimal treatment offered immediately allowed long term preservation of a good clinical condition in most patients, and in many lung transplantation would no longer be necessary. It has already been shown that neonatal screening for cystic fibrosis is feasible without side effects[20–23]; with the development of new therapeutic possibilities[24] we advocate that patients with cystic fibrosis should be detected by means of neonatal screening and treated at specialised cystic fibrosis clinics.

We are indebted to the Netherlands Praeventiefonds which supported this study during nearly 10 years (grants 28.566 and 28.566-1). We thank Symon Terpstra and Jacob Dankert for their helpful comments, never ending support, and stimulating discussions. We thank Jan Schouten and Vacek Fidler for their helpful discussions on the regression analysis. We acknowledge the help of the Dutch Cystic Fibrosis registration for finding all patients from the area. We are grateful to all patients and paediatricians without whom this study would not have been possible. We gratefully acknowledge Ms Carole Lasham for reviewing the English language.

1 Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease. A clinical and pathological study. *Am J Dis Child* 1938;**56**:344–99.
2 Elborn JS, Shale DJ, Britton JR. Cystic fibrosis: current survival and population estimates to the year 2000. *Thorax* 1991;**46**:881–5.
3 Dankert-Roelse JE, te Meerman GJ, Martijn A, ten Kate LP, Knol K. Survival and clinical outcome in patients with cystic fibrosis, with or without neonatal screening. *J Pediatr* 1989;**114**:362–7.
4 Wilcken B, Chalmers G. Reduced morbidity in patients with cystic fibrosis detected by neonatal screening. *Lancet* 1985;ii:1319–21.
5 Shale DJ. Management of cystic fibrosis in different countries. Introduction. *Thorax* 1991;**46**:382–90.
6 Ten Kate LP, Feenstra-de Gooyer J, Ploeg-de Groot G, Gouw WL, Anders BJPA. Should we screen all newborns for cystic fibrosis? *Int J Epidemiol* 1978;7:323–30.
7 Dankert-Roelse JE, te Meerman GJ, Martijn A, ten Kate LP, Knol K. Screening for cystic fibrosis: a comparative study. *Acta Paediatr Scand* 1987;**76**:209–14.
8 Collée JM, Cobben JM, ten Kate LP. Survival of cystic fibrosis patients in the Netherlands. *Proceedings 11th International CF Congress, Dublin* 1992;TP 104.
9 Van Wieringen JC, Wafelbakker F, Verbrugge HP, de Haas SH. *Growth diagrams, 1965, Netherlands*. Nederlands Instituut Praeventieve Geneeskunde, TNO Leiden, Groningen, The Netherlands: Wolters-Noordhoff, 1971.
10 Tammeling GJ. *Standard values for lung volume and ventilatory capacity of sanatorium patients*. Vol I Selected paper of the Royal Netherlands Tuberculosis Association, 1961:65.
11 Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis* 1958;**81**:699–712.
12 Dodge JA, Goodall J, Geddes D, Littlewood JM, Mearns M, Owen JR, *et al.* Cystic fibrosis in the United Kingdom 1977–1985. An improving picture. *BMJ* 1988;**297**:1599–602.
13 Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med* 1992;**326**:1187–91.
14 Davis PB. Cystic fibrosis from bench to bedside. *N Engl J Med* 1991;**325**:575–7.
15 Hoiby N. Hemophilus influenzae, Staphylococcus aureus, Pseudomonas cepacia, and Pseudomonas aeruginosa in patients with cystic fibrosis. *Chest* 1988;**94**:97–102.
16 Weaver LT, Green MR, Nicholson K, Mills J, Heeley ME, Kuzemko JA, *et al.* Prognosis in cystic fibrosis treated with continuous flucloxallin from the neonatal period. *Arch Dis Child* 1994;**70**:84–9.
17 Bronstein MN, Sokol RJ, Abman SH, Chatfield BA, Hammond KB, Hambidge KM, *et al.* Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. *J Pediatr* 1992;**120**:533–40.
18 Marcus MS, Sondel SA, Farrell PM, Laxova A, Carey PM, Langhough R, *et al.* Nutritional status of infants with cystic fibrosis associated with early diagnosis and intervention. *Am J Clin Nutr* 1991;**54**:578–85.
19 Corey M, McLaughlin FJ, Williams M, Levison H. A comparison of survival, growth and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;**41**:583–91.
20 Ranieri E, Ryall RG, Morris CP, Nelson PV, Carey WF, Pollard AC. Neonatal screening strategy for cystic fibrosis using immunoreactive trypsinogen and direct gene analysis. *BMJ* 1991;**302**:1237–40.
21 Ranieri E, Lewis BD, Gerace RL, Ryall RG, Morris PC, Nelson PV, *et al.* Neonatal screening for cystic fibrosis using immunoreactive trypsinogen and direct gene analysis: four years' experience. *BMJ* 1994;**308**:1469–72.
22 Hammond KB, Abman SH, Sokol RJ, Accurso FJ. Efficacy of statewide neonatal screening for cystic fibrosis by assay of trypsinogen concentrations. *N Engl J Med* 1991;**325**:769–74.
23 Green MR, Weaver T, Heeley AF, Nicholson K, Kuzemko JA, Barton DE, *et al.* Cystic fibrosis identified by neonatal screening: incidence, genotype, and early natural history. *Arch Dis Child* 1993;**68**:464–7.
24 Rosenstein BJ, Flotte TR. New directions in treatment. In: Dodge J, Brock DJH, Widdicombe JH, eds. *Current topics in cystic fibrosis*, Vol 1. Chichester: Wiley and Son, 1993:269–301.